PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/001781	21.02.2005	19.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D333/20, C07D333/22, C07C213/00, C07B53/00

Applicant
LONZA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001781

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The present application relates to a process for the preparation of salts of carboxylic acids with an aminoalcohol of the formula Ia/Ib comprising asymmetrically hydrogenating a salt of a carboxylic acid with an aminoketone of the formula II in the presence of a transition metal complex of an aryl- or biaryldiphosphine ligand.

V.2 Reference is made to the following documents:

D1: ROBERTSON D W ET AL: "ABSOLUTE CONFIGURATIONS AND PHARMACOLOGICAL ACTIVITIES OF THE OPTICAL ISOMERS OF FLUOXETINE, A SELECTIVE SEROTONIN-UPTAKE INHIBITOR" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 31, no. 7, 1 July 1988 (1988-07-01), pages 1412-1417, XP000568845 ISSN: 0022-2623

D2: US-A-6 008 412

D3: SAKURABA S ET AL: "EFFICIENT ASYMMETRIC HYDROGENATION OF BETA- AND GAMMA-AMINO KETONE DERIVATIVES LEADING TO PRACTICAL SYNTHESIS OF FLUOXETINE AND EPROZINOL" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 43, no. 5, 1995, pages 748-753, XP001071298 ISSN: 0009-2363

D4: "Prepn. of optically active beta-aminoalcohol - by asymmetric hydrogenation of acid salt of 1-phenyl-3-amino:propanone using metal complex catalyst having phosphino:pyrrolidine ligands" DERWENT, no. 131254, 1993, XP002293166 LONDON GB

D5: EP-A-0 457 559

D6: WO 2004/005239 A

D7: WO 2004/005307 A

V.3 Novelty

Document D1 discloses a salt of a carboxylic acid with an aminoalkohol of formula I

(oxalate salt of compound of formula 2, page 1416, column 1, paragraph 6).
Document D2 discloses a salt of a carboxylic acid with an aminoalkohol of formula I (mandelic acid of N-methyl and N,N-dimethyl-3-hydroxy-3-phenylpropylamine, claims 3, 4, 7 and 8).
Documents D3 and D4 disclose an asymmetric hydrogenation of hydrochloride acid salt with an aminoketone of the formule 3b in the presence of a transition metal complex of an biaryldiphosphine ligand (table 1 and figure 1).
Document D5 discloses hydrochloride salts of aminoketone and suggests further possible acids on page 5, paragraph 1.
Document D6 discloses salts of carboxylic acid with an amino alkohol of formula I in which R1 is however a 2-thienyl group and the acids are the acids excluded in the claim.
Document D7 discloses salts of proton acids with amino alkohols.

A process for the preparation of salts of a carboxylic acid with an aminoalkohole of formula Ia/Ib is disclosed in none of the documents. Claims 1-7 therefore fulfill the requirements of Art 33(2) PCT.

A salt of a carboylic acid with an aminoketone of formula II is disclosed in none of the documents. Claims 8 and 9 therefore fulfill the requirements of Art 33(2) PCT.

Salts of a carboxylic acid with an aminoalkohol of formula II are disclosed in documents D1 and D2. Claim 10 therefore does not fulfill the requirements of Art 33(2) PCT.

V.4 Inventive step

Starting from documents D3 and D4 the problem to be solved by the present application may be regarded as how to provide an alternative process for the preparation of optically active salts with aminoalcohols of formula Ia/Ib. The only difference between the process disclosed in documents D3 and D4 and that of the present application recides in the different acid forming a salt with the starting material. In documents D3 and D4 the acid is hydrochloride acid; in the present application carboxylic acids. This solution seems to be obvious in view of document

D5. Although this document discloses explicitly solely hydrochloride acid salts of aminoketones, further possible acids are suggested in a list on page 5, paragraph 1. Furthermore comparative example 2 of the present application providing an asymmetric hydrogenation of hydrochloride salts shows similar results when compared with asymmetric hydrogenation of carboxylic acid salts of ketones. The present process does not seem to provide any improvement over the prior art process of documents D3 and D4. Thus, the person skilled in the art faced with a problem stated above would probably try to use other acids suggested by D5 to form salts of aminoketones of formula II in an asymmetric hydrognation with a reasonable expectation of success. The solution proposed therefore seems to be obvious in view of prior art documents D3-D5. Inventive step can therefore not be acknowledged for the present application (Art 33(3) PCT).